Efficacy of a bivalent (D614 + B.1.351) SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant in adults: a phase 3, parallel, randomised, modified double-blind, placebo-controlled trial

Gustavo H Dayan, Nadine Rouphael*, Stephen R Walsh*, Aiying Chen, Nicole Grunenberg, Mary Allen, Johannes Antony, Kwaku Poku Asante, Amit Suresh Bhate, Tatiana Beresnev, Matthew I Bonaparte, Médéric Celle, Maria Angeles Ceregido, Lawrence Corey, Dmytro Dobrianskyi, Bo Fu, Marie-Helene Grillet, Maryam Keshtkar-Jahromi, Michal Juraska, Jia Jin Kee, Hannah Kibuuka, Marguerite Koutsoukos, Roger Masotti, Nelson L Michael, Kathleen M Neuzil, Humberto Reynales, Merlin L Robb, Sandra M Villagómez Martínez, Fredrick Sawe, Lode Schuerman, Tina Tong, John Treanor, T Anh Wartel, Carlos A Diazgranados, Roman M Chicz, Sanjay Gurunathan, Stephen Savarino, Saranya Sridhar, on behalf of the VAT00008 Study Team†*

Summary

Background COVID-19 vaccines with alternative strain compositions are needed to provide broad protection against newly emergent SARS-CoV-2 variants of concern. This study aimed to describe the clinical efficacy and safety of a bivalent SARS-CoV-2 recombinant protein vaccine as a two-injection primary series during a period of circulation of the omicron (B.1.1.529) variant.

Methods We conducted a phase 3, parallel, randomised, modified double-blind, placebo-controlled trial in adults aged 18 years or older at 54 clinical research centres in eight countries (Colombia, Ghana, India, Kenya, Mexico, Nepal, Uganda, and Ukraine). Participants were recruited from the community and randomly assigned (1:1) by use of an interactive response technology system to receive two intramuscular 0·5 mL injections, 21 days apart, of the bivalent vaccine (5 µg of ancestral [D614] and 5 µg of beta [B.1.351] variant spike protein, with AS03 adjuvant) or placebo (0·9% normal saline). All participants, outcome assessors, and laboratory staff performing assays were masked to group assignments; those involved in the preparation and administration of the vaccines were unmasked. Participants were stratified by age (18–59 years and ≥60 years) and baseline SARS-CoV-2 rapid serodiagnostic test positivity. Symptomatic COVID-19 was defined as laboratory-confirmed (via nucleic acid amplification test or PCR test) COVID-19 with COVID-19-like illness symptoms. The primary efficacy endpoint was the clinical efficacy of the bivalent vaccine for prevention of symptomatic COVID-19 at least 14 days after the second injection (dose 2). Safety was assessed in all participants receiving at least one injection of the study vaccine or placebo. This trial is registered with ClinicalTrials.gov (NCT04904549) and is closed to recruitment.

Findings Between Oct 19, 2021, and Feb 15, 2022, 13 002 participants were enrolled and randomly assigned to receive the first dose of the study vaccine (n=6512) or placebo (n=6490). 12 924 participants (6472 in the vaccine group and 6452 in the placebo group) received at least one study injection, of whom 7542 (58·4%) were male and 9693 (75·0%) were SARS-CoV-2 non-naive. Of these 12 924 participants, 11 543 (89·3%) received both study injections (5788 in the vaccine group and 5755 in the placebo group). The efficacy-evaluable population after dose 2 comprised 11 416 participants (5736 in the vaccine group and 5680 in the placebo group). The median duration of follow-up was 85 days (IQR 50–95) after dose 1 and 58 days (29–70) after dose 2. 121 symptomatic COVID-19 cases were reported at least 14 days after dose 2 (32 in the vaccine group and 89 in the placebo group), with an overall vaccine efficacy of 64·7% (95% CI 46·6 to 77·2). Vaccine efficacy against symptomatic COVID-19 was 75·1% (95% CI 56·3 to 86·6) in SARS-CoV-2 non-naive participants and 30·9% (–39·3 to 66·7) in SARS-CoV-2-naive participants. Viral genome sequencing identified the infecting strain in 68 (56·2%) of 121 cases (omicron [BA.1 and BA.2] in 63; delta in four; and both omicron and delta in one). Immediate unsolicited adverse events were reported by four (<0·1%) participants in the vaccine group and seven (0·1%) participants in the placebo group. Immediate unsolicited adverse reactions within 30 min after any injection were reported by four (<0·1%) participants in the vaccine group and six (<0·1%) participants in the placebo group. In the reactogenicity subset with available data, solicited reactions (solicited injection-site reactions and solicited systemic reactions) within 7 days after any injection occurred in 1398 (57·8%) of 2420 vaccine recipients and 983 (40·9%) of 2403 placebo recipients. Grade 3 solicited reactions were reported by 196 (8·1%; 95% CI 7·0 to 9·3) of 2420 vaccine recipients and 118 (4·9%; 4·1 to 5·9) of 2403 placebo recipients within 7 days after any injection, with comparable frequencies after dose 1 and dose 2 in the vaccine group. At least one serious adverse event occurred in 30 (0·5%) participants in the vaccine group and 26 (0·4%) in the placebo group. The proportion of adverse events of special interest and deaths was less than 0·1% in both study groups. No adverse event of special interest, serious adverse event, or death was deemed to be treatment related. There were no reported cases of thrombosis with

Lancet Respir Med 2023

Published Online September 13, 2023 https://doi.org/10.1016/S2213-2600(23)00263-1

See Online/Comment https://doi.org/10.1016/S2213-2600(23)00290-4

*Contributed equally

†Members of the VAT00008 Study Team are listed at the end of the Article

Sanofi, Swiftwater, PA, USA (G H Dayan MD, A Chen PhD, M I Bonaparte PhD, R Masotti MS, C A Diazgranados MD, S Gurunathan MD, S Savarino MD); **Emory University Hope Clinic, Atlanta, GA, USA** (Prof N Rouphael MD); **Harvard Medical School, Boston, MA, USA** (S R Walsh MD); **Fred Hutchinson Cancer Center, Seattle, WA, USA** (N Grunenberg MD, Prof L Corey MD, M Juraska PhD, J J Kee MS); **National Institute of Allergy and Infectious Diseases / National Institutes of Health, Bethedsa, MD, USA** (M Allen MS, T Beresnev MD, B Fu PhD, T Tong DrPH); **Sanofi, Frankfurt, Germany** (J Antony PhD); **Research and Development Division, Ghana Health Service, Kintampo North Municipality, Ghana** (K P Asante PhD); **Jeevan Rekha Hospital, Belgavi, India** (A S Bhate MD); **Sanofi, Marcy l'Etoile, France** (M Celle MD); **GlaxoSmithKline, Wavre, Belgium** (M A Ceregido PhD, M Koutsoukos MS, L Schuerman MD); **Medical Centre, Medical Clinic Blagomed, Kyiv, Ukraine**

(D Dobrianskyi MD); **Sanofi, Lyon, France** (M-H Grillet MD); **National Institutes of Health, Rockville, MD, USA** (M Keshtkar-Jahromi MD); **John Hopkins University School of Medicine, Baltimore, MD, USA** (M Keshtkar-Jahromi); **Makerere University Walter Reed Project, Kampala, Uganda** (H Kibuuka MD); **Walter Reed Army Institute of Research, Silver Spring, MD, USA** (N L Michael MD); **University of Maryland School of Medicine, Baltimore, MD, USA** (Prof K M Neuzil MD); **Centro de Attencion e Investigation Medica S.A.S. – Caimed Chía, Chía, Colombia** (H Reynales PhD); **The Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, MA, USA** (M L Robb MD); **Hospital de Temixco en acuerdo con el Instituto Nacional de Pediatria, Temixco, México** (S M Villagómez Martínez MD); **Kenya Medical Research Institute — US Army Medical Research, Kericho, Kenya** (F Sawe MMed); **Tunnell Government Services in support of Biomedical Advanced Research and Development Authority, Administration for Strategic Preparedness and Response, Department of Health and Human Services, Washington, DC, USA** (J Treanor MD); **International Vaccine Institute, Seoul, South Korea** (T A Wartel MD); **Sanofi, Cambridge, MA, USA** (R M Chicz PhD); **Sanofi, Reading, UK** (S Sridhar DPhil)

Correspondence to:
Dr Gustavo H Dayan, Sanofi, Swiftwater, PA 18370, USA
gustavo.dayan@sanofi.com

thrombocytopenia syndrome, myocarditis, pericarditis, Bell's Palsy, or Guillain–Barré syndrome, or other immune-mediated diseases.

Interpretation **The bivalent variant vaccine conferred heterologous protection against symptomatic SARS-CoV-2 infection in the epidemiological context of the circulating contemporary omicron variant. These findings suggest that vaccines developed with an antigen from a non-predominant strain could confer cross-protection against newly emergent SARS-CoV-2 variants, although further investigation is warranted.**

Funding **Sanofi, US Biomedical Advanced Research and Development Authority, and the US National Institute of Allergy and Infectious Diseases.**

Introduction

COVID-19 vaccines were originally developed with the Spike (S) sequence from the SARS-CoV-2 ancestral Wuhan-Hu-1 (D614) strain.[1] However, currently available vaccines are less effective against COVID-19 due to newly emergent SARS-CoV-2 variants of concern (including the omicron [BA.1, BA.2, BA.4, and BA.5] variants and subvariants [BQ.1.1 and XBB]).[2–8] Therefore, vaccines with variant strains have been developed subsequently to provide cross-protection against emerging variants. One strategy for variant vaccine composition is inclusion of the prevalent circulating strain, with mRNA bivalent vaccines containing the omicron variant authorised as boosters on the basis of demonstrated induction of antibodies to circulating omicron variants.[9,10] However, no data are available on whether an alternative non-omicron variant vaccine can provide cross-protective efficacy against omicron variants.

Sanofi and GlaxoSmithKline (GSK) have developed a bivalent vaccine containing stabilised SARS-CoV-2 pre-fusion S proteins from both the ancestral D614 and the beta (B.1.351) variant, with the GSK AS03 adjuvant system (CoV2 preS dTM-AS03 [D614+B.1.351]). This bivalent vaccine is being evaluated as a two-injection primary series in previously unvaccinated individuals and as a booster vaccine in individuals with previous

Research in context

Evidence before this study

We searched PubMed from database inception to Dec 20, 2022, with no language restrictions, for studies reporting the efficacy or effectiveness of vaccines against emergent SARS-CoV-2 variants, including omicron (B.1.1.529), using the search terms "vaccine", "efficacy OR effectiveness", "SARS-CoV-2", "omicron OR variant of concern OR emerging variant", and "clinical trial", and for studies reporting data from updated or bivalent vaccine candidates using the search terms "updated vaccine OR bivalent OR adapted vaccine", "SARS-CoV-2", "omicron OR variant of concern OR emerging variant" AND "clinical trial". Among the observational cohort studies retrieved, first-generation COVID-19 vaccines were shown to be less effective against new emergent SARS-CoV-2 variants of concern, including omicron (BA.1, BA.2, BA.4, and BA.5). Vaccines with different SARS-CoV-2 variant strains have been developed to provide cross-protection against emerging variants when used as boosters; however, there are no data on these vaccines when used as a primary series. Sanofi and GlaxoSmithKline (GSK) have developed a bivalent vaccine containing stabilised SARS-CoV-2 pre-fusion S proteins from both the ancestral Wuhan-Hu-1 (D614) and the beta (B.1.351) variant, with the GSK AS03 adjuvant system (CoV2 preS dTM-AS03 [D614+B.1.351]).

Added value of this study

These data are, to the best of our knowledge, the first to be published suggesting that a primary series with a beta variant vaccine provides cross-protective efficacy against omicron variants. In this phase 3 parallel, randomised, modified double-blind, placebo-controlled trial, overall vaccine efficacy against symptomatic COVID-19 in the epidemiological context of omicron BA1 and BA2 circulation was 64·7% (95% CI 46·6–77·2). Genomic sequencing was available in approximately 56·2% of cases, with BA.1 and BA.2 subvariants of omicron identified as the causative strains in the majority of cases. In additional sensitivity analyses, vaccine efficacy against symptomatic COVID-19 caused by omicron or undefined variants was 63·1% (95% CI 43·9–76·2). In non-naive participants, vaccine efficacy against symptomatic COVID-19 caused by omicron or undefined variants was 73·8% (95% CI 53·9–85·9).

Implications of all the available evidence

To the best of our knowledge, this is the first international phase 3, randomised controlled trial to demonstrate the clinical efficacy of a vaccine containing a beta variant to protect against different SARS-CoV-2 variants, including omicron (BA.1 and BA.2), in non-naive individuals. These results suggest that AS03-adjuvant vaccines developed with an antigen that is not present in the prevalent circulating strain could confer cross-protection in the current context of widely circulating omicron subvariants. These findings warrant further investigation in light of the expected highly variable and unpredictable viral epidemiology of SARS-CoV-2. These findings are relevant given that although approximately 50 vaccines for COVID-19 have been approved worldwide, around a third of the global population has still not been vaccinated.

natural SARS-CoV-2 infection on the basis of preclinical studies showing induction of cross-neutralising antibody responses against a broad panel of variants of concern.[11] The first-in-human results supported selection of the AS03 adjuvant system and a two-injection schedule.[12] The phase 2 results showed acceptable safety and reactogenicity with two doses of the bivalent vaccine, and robust immunogenicity in SARS-CoV-2-naive and non-naive adults, and supported progression to phase 3 evaluation of the 10 µg antigen dose for primary vaccination and a 5 µg antigen dose for booster vaccination.[13] Here, we describe the clinical efficacy and safety of the bivalent variant vaccine as a primary series during a period of omicron circulation.

Methods

Study design and participants

This phase 3, parallel, randomised, modified double-blind, placebo-controlled trial was designed as a two-stage platform study. Stage 1 evaluated the efficacy and safety of the prototype vaccine, containing the ancestral D614 recombinant S protein (CoV2 preS dTM-AS03 [D614]).[14] Stage 2, reported here, evaluated the efficacy and safety of a primary series of two injections of the bivalent vaccine, administered 21 days apart. Stage 2 was conducted in 54 clinical research centres across eight countries: Colombia, Ghana, India, Kenya, Mexico, Nepal, Uganda, and Ukraine (appendix pp 3–4). Participant enrolment started on Oct 19, 2021, and finished on Feb 15, 2022.

The study was conducted in compliance with the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol and amendments were approved by applicable independent ethics committees and institutional review boards and as per local regulations (appendix p 5). All participants provided written informed consent that was not subject to any conditions.

Adults aged 18 years or older who had not previously received a COVID-19 vaccine were eligible for inclusion; full details of the inclusion and exclusion criteria are reported in the appendix (p 6). Since approved and authorised COVID-19 vaccines were already available in some countries and regions where the study was conducted, investigators discussed the availability of these vaccines with participants, encouraged them to obtain the approved or authorised vaccine as applicable, and proceeded with enrolment only if, despite encouragement, the participant expressed no interest in seeking approved or authorised COVID-19 vaccines. Furthermore, participants were counselled at each opportunity about the availability and benefits of the approved vaccines. Participants were allowed to receive an authorised vaccine outside the study protocol and were offered the option to continue in the study for safety and immunogenicity follow-ups. Participants potentially at high risk of severe COVID-19 (appendix p 7) and other subpopulations at risk of COVID-19, including ethnic and racial minorities, were included. Data on self-reported medical history, sex, ethnicity, and race were collected at the time of enrolment.

Randomisation and masking

Eligible participants were randomly assigned (1:1) to receive either the bivalent vaccine or placebo (saline). Randomisation was done with an interactive response technology system (IRT). Stratified permuted sub-block randomisation with a block size of eight (four vaccine and four placebo) was applied for study group randomisation, in which strata were age group (18–59 years or ≥60 years), baseline SARS-CoV-2 rapid serodiagnostic test positivity (positive and negative), and study site. Site staff entered identification and security information and confirmed a minimal amount of data in response to IRT prompts. The IRT then provided a group assignment and assigned a 12-digit participant number. All participants, outcome assessors, and laboratory staff performing assays were masked to group assignments; site staff involved in the preparation and administration of the vaccines were unmasked, but they were not involved in study outcome assessments.

Procedures

See Online for appendix

The recombinant protein antigen CoV2 preS dTM, stabilised in its prefusion form and produced with the baculovirus expression system technology, and the AS03 adjuvant system (GSK Vaccines, Rixensart, Belgium) have been described previously.[12,13,15] Each 0·5 mL injection of the bivalent vaccine formulation contained 5 µg of the ancestral D614 and 5 µg of the B.1.351 variant S protein antigen. The CoV2 preS dTM antigen and AS03 adjuvant were presented in two separate vials: a multidose vial containing AS03 (sufficient for ten injections) and a multidose vial containing the S protein antigen (ten doses of 5 µg D614+5 µg B.1.351). An equal volume of the adjuvant emulsion was added to the vial containing the antigen and mixed before injection. At each vaccination, participants in the vaccine group received one 0·5 mL injection containing the bivalent vaccine and participants in the placebo group received one 0·5 mL injection of 0·9% normal saline. Vaccinations were administered on study days 1 and 22 by intramuscular injection into the deltoid region by qualified and trained personnel.

Blood samples and nasopharyngeal swabs were collected before each vaccination to establish whether participants had previous or ongoing SARS-CoV-2 infection (ie, whether they were SARS-CoV-2-naive or non-naive).

Surveillance for COVID-19-like illness was both active and passive: participants were contacted once a week to determine whether they had any symptoms of a

COVID-19-like illness (appendix p 8) or whether they had a positive COVID-19 test from another source at any time during the study. Participants were also instructed to contact their respective study site if they experienced symptoms of a COVID-19-like illness or if they had a positive COVID-19 test from any other source at any time during the study. In the event of symptoms of a COVID-19-like illness, nasopharyngeal and anterior nasal swabs were collected at the participant's first visit after symptom onset and 2–4 days later for virological confirmation with nucleic-acid amplification tests. Further anterior nasal swabs were collected 7–9 days and 12–14 days after the first illness visit. If any specimen was found to be positive for SARS-CoV-2, the participant was asked to continue recording their daily COVID-19 symptoms until the end of their illness or for up to 30 days from symptom onset. If symptoms persisted for more than 30 days, participants were asked to record the date when the symptoms resolved. An independent adjudication committee reviewed potential cases to determine whether the case definitions for symptomatic or severe COVID-19 were met. Viral genomic sequencing was done on respiratory samples from confirmed cases to identify the SARS-CoV-2 variant, as previously described.[16]

Participants were classified as naive or non-naive by assessment of blood samples through Elecsys electrochemiluminescence immunoassays for detection of anti-S antibodies (Elecsys Anti-SARS-CoV-2 S assay; Roche, Indianapolis, IN, USA) on study day 1 and for detection of anti-nucleocapsid antibodies (Elecsys Anti-SARS-CoV-2 N; Roche, Indianapolis, IN, USA) on study days 1 and 22; and for detection of SARS-CoV-2 nucleic acids in nasopharyngeal swabs by use of nucleic-acid amplification tests (Abbott RealTime SARS-CoV-2 assay; Abbott Molecular, Des Plaines, IL, USA) on study days 1 and 22. Testing procedures and criteria for determination of previous SARS-CoV-2 infection are described in the appendix (p 9).

Outcomes

The primary efficacy endpoint was the clinical efficacy of the bivalent vaccine for prevention of symptomatic COVID-19 at least 14 days after the second injection (ie, after dose 2) in all participants, regardless of previous infection. Secondary efficacy endpoints included the occurrence of symptomatic disease in naive and non-naive individuals; severe, moderate, or worse disease; or admission to hospital for COVID-19 at least 14 days after dose 2 in all participants and according to previous infection status. The impact of sex, age (18–59 years or ≥60 years), and high-risk medical conditions on the above outcomes was evaluated as pre-defined exploratory endpoints. Other analyses included the occurrence of symptomatic or severe COVID-19 at least 14 days after the first injection. The occurrence of asymptomatic infection in SARS-CoV2-naive participants was also assessed. Definitions of COVID-19 efficacy outcomes are reported in the appendix (pp 10–11).

Participants were directed to report any adverse events during their study visits or during any follow-up contact with the investigators. Safety data were collected from all participants receiving at least one injection of the study vaccine or placebo throughout the duration of the study (appendix p 12). Solicited injection-site reactions and solicited systemic reactions occurring within 7 days after each vaccination, and non-serious unsolicited adverse events occurring within 21 days after each vaccination, were collected in a subset of approximately 4000 participants (the first 4000 participants recruited [2000 in each group]) as well as all participants aged ≥60 years.

Statistical analysis

The data cutoff date for the analyses reported here was March 15, 2022, when the number of cases for the prespecified event-driven analysis was reached. Calculations for determining this sample size are reported in the appendix (p 13). It was estimated that a sample of 10 886 participants would be required, with approximately 125 symptomatic COVID-19 cases needed to achieve 80% statistical power. The planned target for SARS-CoV-2 non-naive participants was approximately 3266 participants (1633 per group). The sample size of 7620 SARS-CoV-2-naive participants was powered independently to achieve the primary endpoint of vaccine efficacy against symptomatic COVID-19 in SARS-CoV-2-naive adults. Given the global epidemiological situation, in which most of the population has already been infected with SARS-CoV-2, the primary population for the assessment of vaccine efficacy was changed from naive participants to all participants who met per-protocol defined criteria. The protocol was amended on April 11, 2022, before the primary efficacy analysis was performed. The updated protocol includes both naive and non-naive individuals for assessment of the primary endpoint.

Therefore, sample size calculations were based on a primary endpoint that considered only naive participants. The power of the primary efficacy analysis was driven by the total number of symptomatic COVID-19 events. The incidence rate of symptomatic COVID-19 in the placebo group was assumed to be 2·25% per 2 months of follow-up. An attrition rate of 30% was expected, as during the conduct of the study a greater proportion of the cohort became eligible to receive locally available authorised COVID-19 vaccines. Because omicron was the prevalent variant during case accrual and the vaccine efficacy against omicron was expected to be lower than the original assumption of 70%, the expected true vaccine efficacy for symptomatic COVID-19 was estimated at 60%. Therefore, a total of approximately 125 symptomatic COVID-19 events was required to achieve 80% power with a one-sided type I error rate of 0·025, assuming no

interim analysis. For interim analyses, the type I error rate was adjusted appropriately. If the planned interim analysis was skipped, or if the information fraction was different from that planned (not within the range of 50–70% of data), alpha splitting was adjusted on the basis of the Lan-DeMets O'Brien-Fleming approximation spending function.

Descriptions of the analysis sets are reported in the appendix (p 14). An independent data and safety monitoring board[17] provided study oversight and reviewed unblinded data. Censoring occurred at random. Patients were censored if they had an early termination during the analysis period (the termination date was the censoring date); received another SARS-CoV-2 vaccine outside the protocol (the date of vaccination was the censoring date); had an event (either a US Centers for Disease Control and Prevention [CDC]-defined event or symptomatic COVID-19 event for a CDC-defined endpoint); or had a symptomatic COVID-19 event for other endpoints (the start date of the event was the censoring date); or, if the participant did not meet any of the above, the cutoff date of the planned analysis was the censoring date.

The randomised group included all participants who were allocated to a treatment group; of these, participants who received at least one study injection were included in the full analysis set. The primary efficacy analyses were conducted, as prespecified, on the modified full analysis set after dose 2, which comprised participants who received both injections (excluding participants with onset of symptomatic COVID-19 between the first injection [after dose 1] and 14 days after dose 2) who did not meet any vaccine contraindications and did not discontinue the study within 14 days after dose 2. The modified full analysis set after dose 1 excluded participants in the full analysis set with onset of symptomatic COVID-19 between the date of the first injection and 14 days after the first injection, or those who discontinued from the study within 14 days after the first injection. Secondary efficacy analyses were conducted in subgroups further divided on the basis of previous infection status after dose 1 and dose 2. Results for participants in the modified full analysis set after dose 1 are also included for comparison, as previous reports with COVID-19 vaccines have shown protection after a single injection.

For the primary endpoint, the point estimate of vaccine efficacy was calculated on the basis of the incidence rate per 1000 person-years per group in the modified full analysis set after dose 2, regardless of previous infection status. The primary objective was met if the vaccine efficacy point estimate was higher than 50% and the lower bound of the confidence interval (95% CI) was higher than 30%.[18] Survival analyses were also done with Kaplan-Meier curves and 95% CIs. As supportive analyses, survival analyses were also done on the basis of a stratified Cox proportional hazards model (based on the baseline strata of age group, sex, high-risk medical condition, and previous SARS-CoV-2 infection status) to estimate vaccine efficacy by one minus the hazard ratio with score-based 95% CI. Sensitivity analyses against symptomatic COVID-19 were prespecified, with vaccine efficacy calculated by relative risk in the modified full analysis set after dose 2 and by the incidence rate ratios (IRRs) of COVID-19 case occurrence in the per-protocol analysis set. Sensitivity analyses were also conducted assuming that unsequenced cases were due to the omicron variant, which was the prevalent variant circulating at the time of the study. Safety outcomes were assessed in the safety analysis set, which comprised all randomised participants who received at least one injection of the study vaccine or placebo. The reactogenicity safety analysis subset comprised participants in the safety analysis set who received at least one study injection, were randomly assigned to the reactogenicity subset, and reported reactogenicity data. The 95% CI for the single proportions was calculated with the exact binomial method (Clopper–Pearson method). Statistical analyses were performed with SAS (version 9.4 or later).

This study is registered with ClinicalTrials.gov (NCT04904549) and trial recruitment has now been completed.

Role of the funding source

The funders were involved in study design, data analysis, data interpretation, writing of the report, and the decision to submit the paper for publication. GSK provided access to, and use of, the AS03 Adjuvant System.

Results

Between Oct 19, 2021, and Feb 15, 2022, 13 506 participants were enrolled and randomly assigned. Owing to the ongoing war in Ukraine, data completeness could not be confirmed for the four Ukrainian sites; therefore, none of the 504 participants from these sites was included in the main analyses (figure 1), although sensitivity analyses including these data were performed.

In the current analysis, 13 002 participants were randomly assigned to receive the study vaccine (n=6512) or placebo (n=6490) up to the data cutoff date for the analyses of March 15, 2022 (figure 1). 12 924 participants (6472 in the vaccine group and 6452 in the placebo group) received the first vaccine dose and were included in the full analysis set (two participants in the placebo group received an injection at visit 1 but it was not recorded whether they received the vaccine or placebo; these participants were excluded from the safety analysis). Of these 12 924 participants, 11 416 (5736 in the vaccine group and 5680 in the placebo group) were included in the modified full analysis set after dose 2. 1508 participants were excluded from the modified full analysis set after dose 2 (736 in the vaccine group and 772 in the placebo group) for the following reasons: 684 participants in the vaccine group and 697 participants in the placebo group

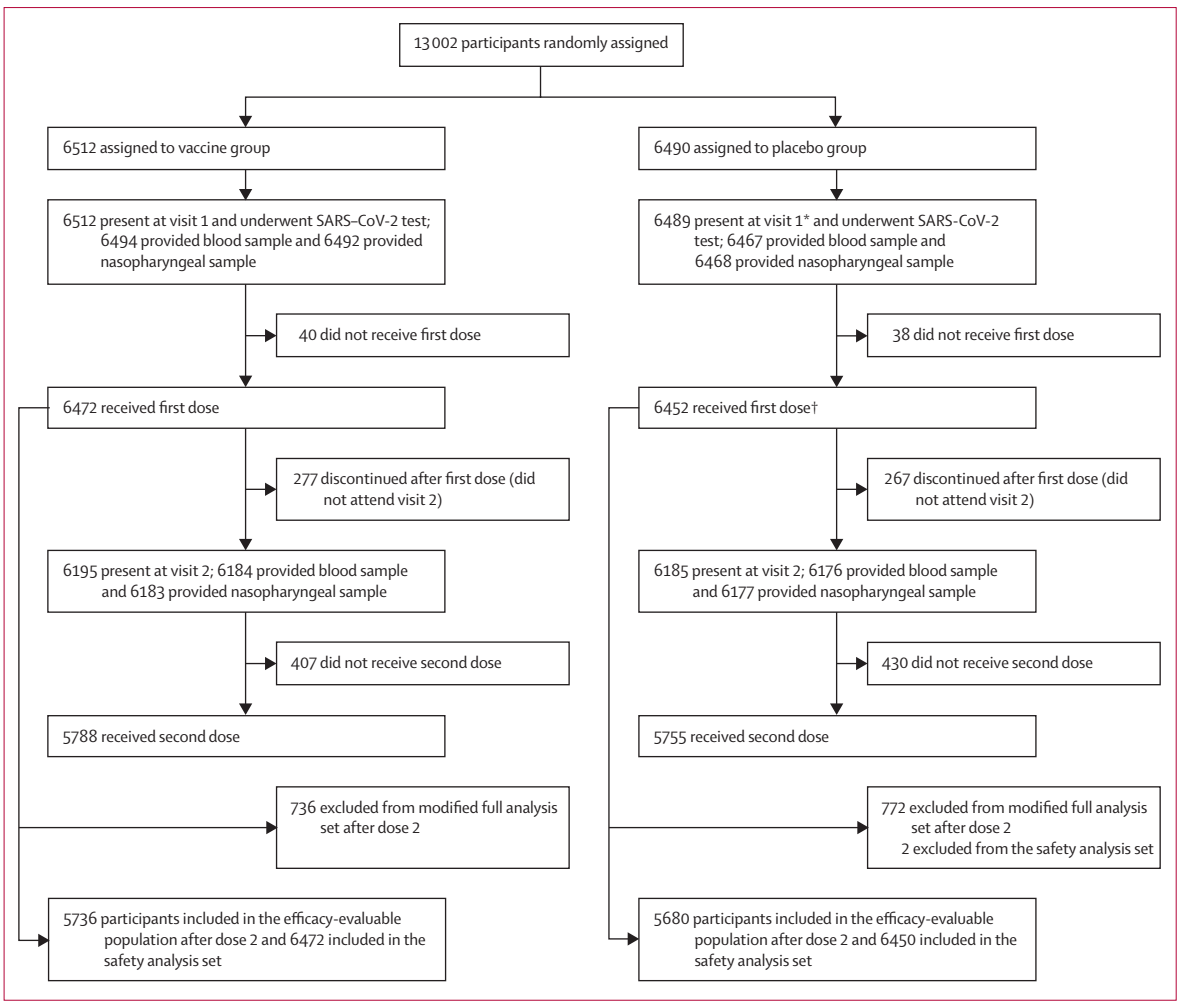


Figure 1: **Trial profile**
12 809 participants (6418 in the vaccine group and 6391 in the placebo group) were included in the modified full analysis set after dose 1. 8643 participants (4327 in the vaccine group and 4316 in the placebo group) completed at least 1 month of follow-up after dose 2. 5453 participants (2731 in the vaccine group and 2722 in the placebo group) completed at least 2 months of follow-up after dose 2. *Visit 1 for one participant did not appear in the database during data extraction on June 9, 2022, because the site was entering additional data for visit 1 at the time the data extraction was performed. However, this participant was included in the modified full analysis set after dose 1, modified full analysis set after dose 2, and non-naive day 1/day 22 analysis sets because both visits 1 and 2 were performed. †Two participants randomly assigned to the placebo group received the first dose but the administered product was unknown. Therefore, they were not included in the safety analysis set (the analysis was performed according to the intervention they actually received).

did not complete the vaccination schedule; 28 participants in the vaccine group and 50 participants in the placebo group had onset of a symptomatic COVID-19 episode between the first date of vaccination and 14 days after the second vaccination; 40 participants received the second vaccination despite meeting one of the definitive contraindication criteria (22 in the vaccine group and 18 in the placebo group); and 14 participants discontinued the study before 14 days after the second vaccination (five in the vaccine group and nine in the placebo group). Participants in the main analysis sets are summarised in the appendix (p 15).

A total of 12 924 participants received at least one study injection, for whom demographic characteristics are reported on the basis of first visit samples (table 1). 4851 participants were included in the reactogenicity safety analysis subset (2433 in the vaccine group and 2418 in the placebo group; appendix p 15). Participant demographics were comparable across treatment groups. The mean age was 36·1 (SD 12·9) years and 7542 (58·4%) participants were male (table 1). High-risk medical conditions were present in 4165 (32·2%) participants (table 1; appendix p 16). 9693 (75·0%) participants had evidence of previous infection (ie, were non-naive) at enrolment (4860 in the vaccine group and 4831 in the placebo group).

In both treatment groups, the longest duration of follow-up was 148 days (median 85 [IQR 50–95]) after dose 1 and 118 days (median 58 [29–70]) after dose 2 (appendix pp 17–18). The proportion of participants with at least 2 months' follow-up at the data cutoff date was 67·4% (8706 of 12 924)

after dose 1 and 47·2% (5453 of 11543) after dose 2. The vast majority of cases in all countries were due to omicron BA.1 and BA.2 (appendix p 19).

The modified full analysis set after dose 2 comprised 11416 participants. 121 symptomatic COVID-19 cases were reported at least 14 days after dose 2 (32 in the vaccine group and 89 in the placebo group), with an overall vaccine efficacy of 64·7% (95% CI 46·6–77·2), which met the primary efficacy endpoint (figure 2). In the sensitivity analysis, vaccine efficacy based on the relative risk of symptomatic COVID-19 case occurrence in the modified full analysis set after dose 2 was 64·2% (95% CI 45·8–76·9 [32 cases in the vaccine group and 89 cases in the placebo group]). In the per-protocol analysis set, vaccine efficacy calculated by the IRR of symptomatic COVID-19 case occurrence was 63·4% (95% CI 44·5–76·4 [32 cases in the vaccine group and 86 cases in the placebo group]). Similar results for the primary endpoint were reported in a sensitivity analysis that included Ukrainian participants (vaccine efficacy 64·0%; 95% CI 45·9–76·6; appendix p 20). The cumulative incidence rate of symptomatic COVID-19 was higher in the placebo group than in the vaccine group starting from 14 days after the second dose (figure 3; appendix pp 21–23). The results of the survival analysis based on the stratified Cox proportional hazards model are reported in the appendix (p 24).

Of 121 symptomatic COVID-19 cases, five participants (three vaccine recipients and two placebo recipients) reported severe COVID-19, and 12 reported moderate or worse symptomatic COVID-19 (five vaccine recipients and seven placebo recipients) occurring from 14 days after dose 2 in the modified full analysis set. Two placebo recipients in the modified full analysis set after dose 2 were admitted to hospital with COVID-19. No deaths associated with COVID-19 were reported.

Vaccine efficacy against symptomatic COVID-19 in non-naive participants was 75·1% (95% CI 56·3 to 86·6), while in naive participants the point estimate for vaccine efficacy was 30·9% (–39·3 to 66·7; figure 2). The cumulative incidence of symptomatic COVID-19 was higher in the placebo group than in the vaccine group starting from 14 days after dose 2 in non-naive and naive participants (figure 3). The number at risk decreased rapidly 74 days after dose 2 (ie, 60+14 days; figure 3) as the majority of participants had their second vaccination after Jan 1, 2022, so were censored on March 15, 2022, which was the cutoff date. The overall vaccine efficacy against symptomatic COVID-19 was 60·3% (95% CI 47·1 to 70·5) after dose 1 (appendix p 25). The higher cumulative incidence of symptomatic COVID-19 in the placebo group started within 14 days in naive, non-naive, and all participants after dose 1 in the modified full analysis set (appendix pp 26–27).

Efficacy results against symptomatic disease in all participants and subgroups are shown in figure 2 and the appendix (pp 28–30). Outcomes with too few cases to reliably calculate vaccine efficacy (severe COVID-19, moderate or worse COVID-19, and hospital admission due to COVID-19) are not shown. Vaccine efficacy could not be reliably estimated in participants aged 60 years and older as only three cases of symptomatic COVID-19 were reported in the vaccine group and two in the placebo group for these participants. Efficacy against asymptomatic SARS-CoV-2 infection (assessed in naive participants only) was 1·2% (95% CI –31·0 to 25·5), with

	Vaccine group (n=6472)	Placebo group (n=6450)	Total (n=12 924*)
Sex			
Male	3789 (58·5%)	3751 (58·2%)	7542 (58·4%)
Female	2683 (41·5%)	2699 (41·8%)	5382 (41·6%)
Mean age, years	36·1 (13·0)	36·0 (12·9)	36·1 (12·9)
Age categories			
18–59 years	6078 (93·9%)	6067 (94·1%)	12147 (94·0%)
≥60 years	394 (6·1%)	383 (5·9%)	777 (6·0%)
Mean BMI (kg/m²)	23·8 (4·61)	23·8 (4·41)	23·8 (4·51)
Race			
American Indian or Alaskan Native	408 (6·3%)	402 (6·2%)	811† (6·3%)
Asian	2562 (39·6%)	2567 (39·8%)	5129 (39·7%)
Black or African American	2873 (44·4%)	2854 (44·2%)	5727 (44·3%)
White	36 (0·6%)	38 (0·6%)	74 (0·6%)
Multiracial	5 (0·1%)	6 (0·1%)	11 (0·1%)
Not reported	95 (1·5%)	82 (1·3%)	177 (1·4%)
Ethnicity			
Hispanic or Latino	1056 (16·3%)	1051 (16·3%)	2109† (16·3%)
Not Hispanic or Latino	5381 (83·1%)	5372 (83·3%)	10753 (83·2%)
Not reported	15 (0·2%)	13 (0·2%)	28 (0·2%)
Country			
Mexico	495 (7·6%)	493 (7·6%)	989 (7·7%)
Colombia	537 (8·3%)	532 (8·2%)	1070 (8·3%)
India	1661 (25·7%)	1672 (25·9%)	3333 (25·8%)
Uganda	212 (3·3%)	206 (3·2%)	418 (3·2%)
Ghana	597 (9·2%)	598 (9·3%)	1195 (9·2%)
Kenya	2066 (31·9%)	2052 (31·8%)	4118 (31·9%)
Nepal	904 (14·0%)	897 (13·9%)	1801 (13·9%)
Previous SARS-CoV-2 infection			
Naive at day 1	588 (9·1%)	588 (9·1%)	1176 (9·1%)
Non-naive at day 1	4860 (75·1%)	4831 (74·9%)	9693 (75·0%)*
Undetermined at day 1	1024 (15·8%)	1031 (16·0%)	2055 (15·9%)
Naive at day 22	333 (5·1%)	350 (5·4%)	683 (5·3%)
Non-naive at day 22	5478 (84·6%)	5486 (85·1%)	10966 (84·8%)
Undetermined at day 22	661 (10·2%)	614 (9·5%)	1275 (9·9%)
High-risk medical condition			
Yes	2095 (32·4%)	2070 (32·1%)	4165 (32·2%)
No	4377 (67·6%)	4380 (67·9%)	8759 (67·8%)

Data are n (%) or mean (SD). *Two participants received a vaccine at visit 1 but whether they received the vaccine or the placebo is unknown. Therefore, there is a difference of two participants in the total number of participants of the safety analysis set. †One of the two participants who had missing information about the vaccine or placebo was American Indian or Alaskan Native. For the other participant, the race was unknown although the ethnicity was Hispanic or Latino.

Table 1: **Demographics and clinical characteristics at baseline in the participants who received at least one injection (safety analysis set)**

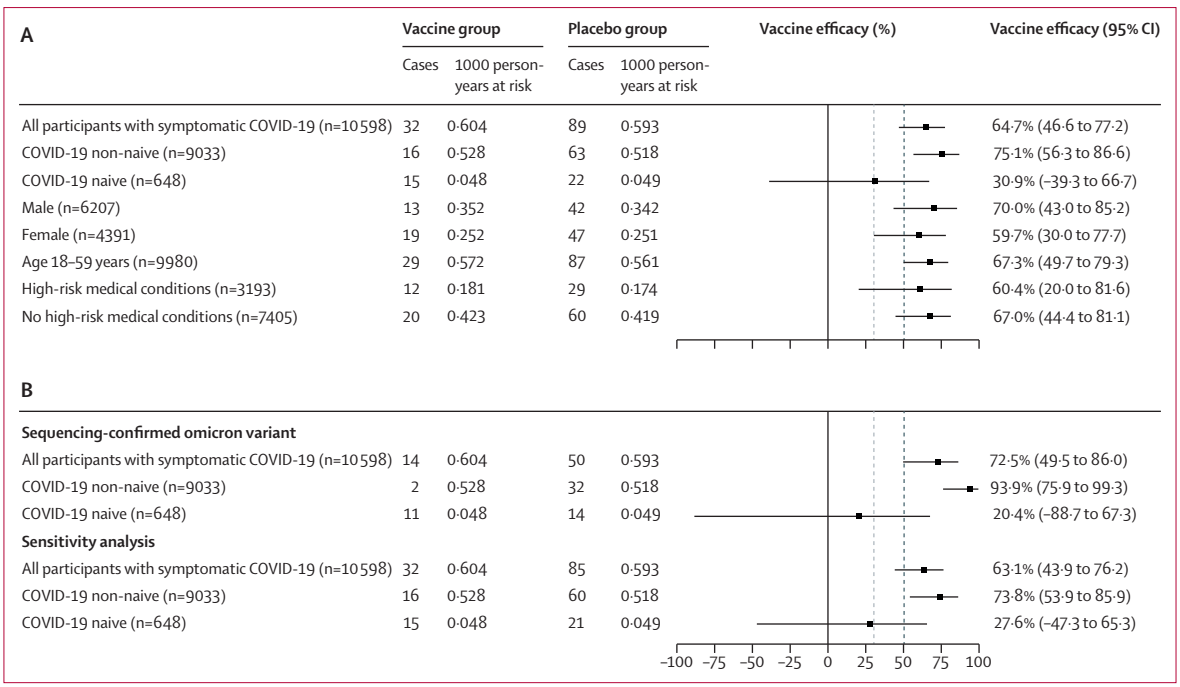


Figure 2: **Efficacy outcomes against symptomatic COVID-19 in all participants and subgroups**
(A) Efficacy outcomes overall (for all variants) and by subgroup for the modified full analysis set after dose 2. The success criterion for demonstration of efficacy was defined as a point estimate higher than 50% (dark grey dotted line) and a lower bound of the 95% CI higher than 30% (light grey dotted line). Outcomes with too few cases to reliably calculate vaccine efficacy (severe COVID-19, moderate or worse COVID-19, hospital admission due to COVID-19, and symptomatic COVID-19 in participants aged ≥60 years) are not shown. (B) Vaccine efficacy for all sequencing-confirmed omicron (B.1.1.529) cases and for the sensitivity analysis, which included sequencing-confirmed cases and cases for which there were no sequencing results, assuming that the latter group of cases were caused by the omicron variant as this was the variant responsible for most of the symptomatic COVID-19 cases at the time of the study. The success criterion for demonstration of efficacy was defined as a point estimate higher than 50% (dark grey dotted line) and a lower bound of the 95% CI higher than 30% (light grey dotted line). Owing to the low number of cases due to the delta variant, these are not shown.

100 cases in the vaccine group and 107 cases in the placebo group (appendix p 31). Overall, vaccine efficacy was higher for male participants (70·0%; 95% CI 43·0 to 85·2) compared with female participants (59·7%;30·0 to 77·7; figure 2).

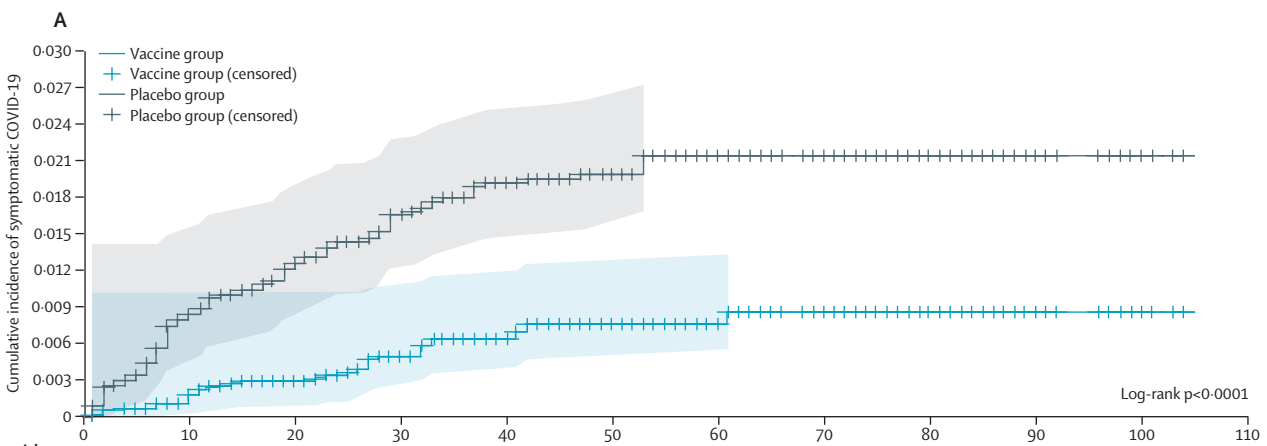
Of the 121 adjudicated cases (32 in the vaccine group and 89 in the placebo group), the causative viral strain was sequenced in 68 (56·2%) cases, with the majority (63 of 68) corresponding to the BA.1 and BA.2 subvariants of omicron (14 cases in the vaccine group and 49 cases in the placebo group) and the others corresponding to the delta (B.1.617.2) variant (four of 68; all in the placebo group). One participant had mixed infection with the omicron and delta variants and was thus included in the analysis for both variants. Results for the other 53 (43·8%) adjudicated cases were not available for several reasons: cases were diagnosed with a local test for which no specimen was available (n=8), the viral load threshold was too low for detection (n=12), the laboratory did not produce a valid result (n=32), or the sample was not tested (n=1). Of the 53 cases with undiagnosed variants, 18 (56·3%) of 32 were in the vaccine group and 35 (39·3%) of 89 were in the placebo group.

Among the 68 sequenced cases, 64 were due to the omicron variant (14 in vaccine recipients and 50 in placebo recipients), with the omicron-specific vaccine efficacy estimated as 72·5% (95% CI 49·5 to 86·0) in all participants (figure 2), 93·9% (75·9 to 99·3) in non-naive participants, and 20·4% (–88·7 to 67·3) in naive participants. Kaplan-Meier analyses showed a higher cumulative incidence of symptomatic COVID-19 due to the omicron variant in the placebo group compared with the vaccine group 14 days after dose 2 (appendix p 32). There were no delta-related COVID-19 cases in the vaccine group, and five cases in the placebo group.

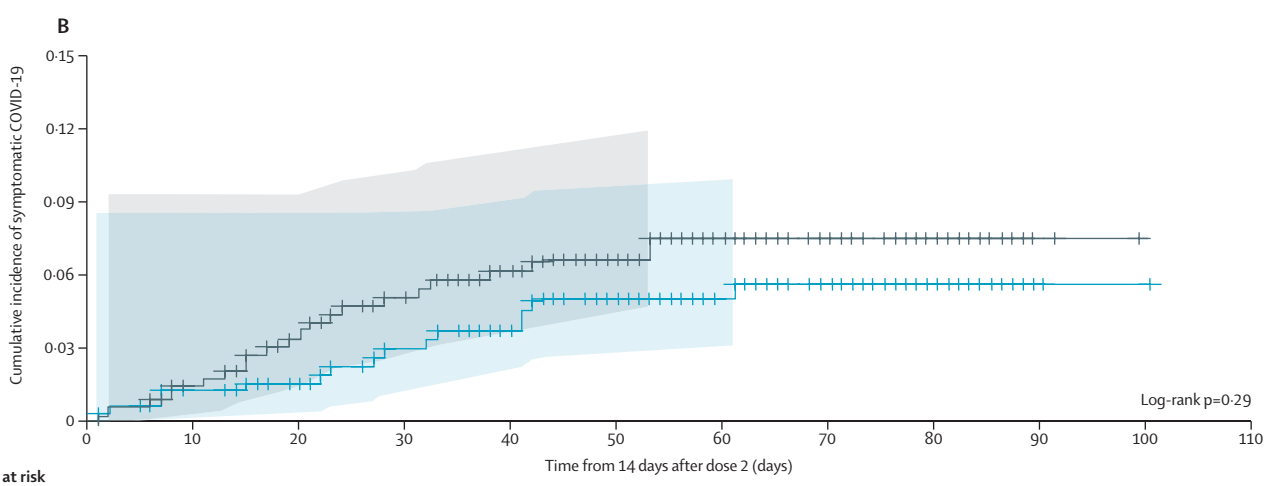
In sensitivity analyses, the vaccine efficacy against symptomatic COVID-19 caused by the omicron or undefined variants (32 cases in the vaccine group, 85 cases in the placebo group) was 63·1% (95% CI 43·9 to 76·2) in all participants, 73·8% (95% CI 53·9 to 85·9) in non-naive participants, and 27·6% (95% CI –47·3 to 65·3) in naive participants (appendix p 33).

A summary of safety outcomes in participants who received at least one injection of vaccine or placebo (ie, the safety analysis set) is reported in table 2 and the appendix (pp 34–36). Immediate unsolicited adverse events were reported by four (<0·1%) participants in the vaccine group and seven (0·1%) participants in the placebo group. Immediate unsolicited adverse reactions within 30 min

after any injection were reported by four (<0·1%) participants in the vaccine group and six (<0·1%) participants in the placebo group. Of the 4823 participants in the reactogenicity subset with available data, solicited reactions (solicited injection-site reactions and solicited systemic reactions) within 7 days after any injection

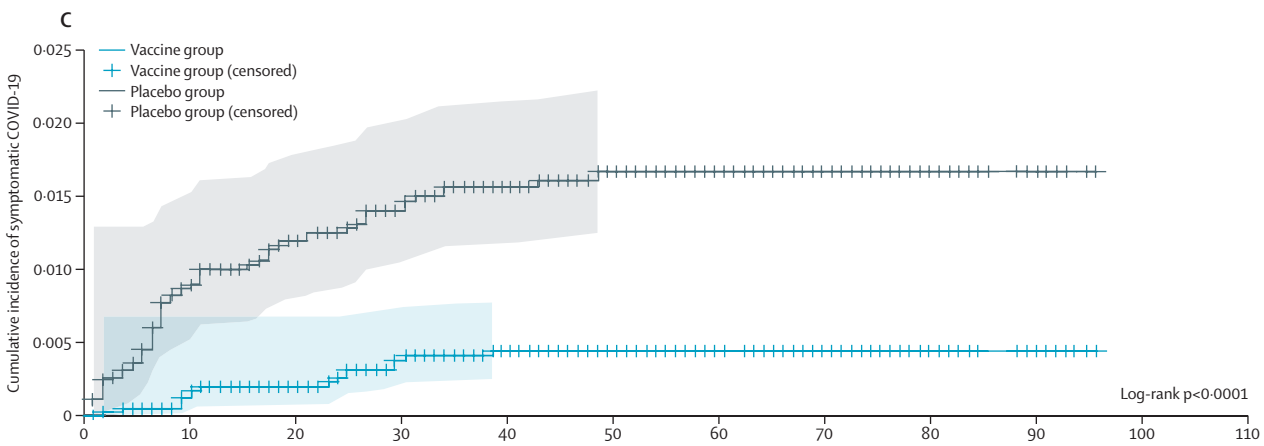


Number at risk (number censored)												
Vaccine group	5311	4512	4142	3604	3295	2227	1017	559	220	30	16	0
	(0)	(793)	(1155)	(1685)	(1989)	(3053)	(4263)	(4720)	(5059)	(5249)	(5263)	(5279)
Placebo group	5287	4441	4071	3519	3232	2169	977	539	219	36	14	0
	(0)	(806)	(1158)	(1693)	(1971)	(3032)	(4221)	(4659)	(4979)	(5162)	(5184)	(5198)
Cumulative events												
Vaccine group	0	9	14	22	27	31	31	32	32	32	32	32
Placebo group	0	42	60	75	84	86	89	89	89	89	89	89
Incidence estimate (95% CI)												
Vaccine group	0	0·002 (0·001–0·010)	0·003 (0·001–0·010)	0·005 (0·002–0·011)	0·006 (0·004–0·012)	0·008 (0·005–0·013)	0·008 (0·005–0·013)	0·009 (0·006–0·013)	0·009 (0·006–0·013)	0·009 (0·006–0·013)	0·009 (0·006–0·013)	0·009 (0·006–0·013)
Placebo group	0	0·008 (0·005–0·016)	0·013 (0·008–0·019)	0·017 (0·012–0·023)	0·019 (0·015–0·025)	0·020 (0·015–0·026)	0·022 (0·017–0·027)	0·022 (0·017–0·027)	0·022 (0·017–0·027)	0·022 (0·017–0·027)	0·022 (0·017–0·027)	0·022 (0·017–0·027)



Number at risk (number censored)											
Vaccine group	315	301	284	260	240	214	161	106	42	2	1
	(0)	(10)	(26)	(46)	(64)	(87)	(140)	(194)	(258)	(298)	(299)
Placebo group	333	313	290	268	244	218	160	87	36	2	0
	(0)	(15)	(32)	(49)	(70)	(95)	(151)	(224)	(275)	(309)	(311)
Cumulative events											
Vaccine group	0	4	5	9	11	14	14	15	15	15	15
Placebo group	0	5	12	16	19	20	22	22	22	22	22
Incidence estimate (95% CI)											
Vaccine group	0	0·013 (0·001–0·086)	0·016 (0·002–0·086)	0·031 (0·011–0·086)	0·038 (0·016–0·088)	0·050 (0·026–0·095)	0·050 (0·026–0·095)	0·056 (0·031–0·100)	0·056 (0·031–0·100)	0·056 (0·031–0·100)	0·056 (0·031–0·100)
Placebo group	0	0·015 (0·002–0·094)	0·038 (0·015–0·094)	0·052 (0·026–0·101)	0·062 (0·035–0·109)	0·066 (0·039–0·112)	0·075 (0·047–0·120)	0·075 (0·047–0·120)	0·075 (0·047–0·120)	0·075 (0·047–0·120)	0·075 (0·047–0·120)

(Figure 3 continues on next page)



Number at risk (number censored)												
Vaccine group	4519 (0)	3909 (608)	3674 (837)	3248 (1259)	2972 (1532)	1937 (2566)	816 (3687)	426 (4077)	171 (4332)	28 (4475)	15 (4488)	0 (4503)
Placebo group	4514 (0)	3846 (633)	3609 (858)	3164 (1294)	2910 (1543)	1896 (2556)	786 (3665)	426 (4025)	179 (4272)	34 (4417)	14 (4437)	0 (4451)
Cumulative events												
Vaccine group	0	5	8	12	15	16	16	16	16	16	16	16
Placebo group	0	37	48	56	61	62	63	63	63	63	63	63
Estimate (95% CI)												
Vaccine group	0	0·001 (0·000–0·007)	0·002 (0·001–0·007)	0·003 (0·001–0·007)	0·004 (0·002–0·008)	0·004 (0·003–0·008)	0·004 (0·003–0·008)	0·004 (0·003–0·008)	0·004 (0·003–0·008)	0·004 (0·003–0·008)	0·004 (0·003–0·008)	0·004 (0·003–0·008)
Placebo group	0	0·009 (0·005–0·015)	0·012 (0·008–0·018)	0·014 (0·010–0·020)	0·016 (0·011–0·021)	0·016 (0·012–0·022)	0·017 (0·012–0·022)	0·017 (0·012–0·022)	0·017 (0·012–0·022)	0·017 (0·012–0·022)	0·017 (0·012–0·022)	0·017 (0·012–0·022)

Figure 3: **Cumulative incidence of symptomatic COVID-19 in the modified full analysis set after dose 2**
(A) Overall. (B) SARS-CoV-2-naive populations. (C) SARS-CoV-2 non-naive populations.

occurred in 1398 (57·8%) of 2420 vaccine recipients and 983 (40·9%) of 2403 placebo recipients (table 2). The solicited injection-site reactions and solicited systemic reactions experienced after each dose are summarised by age categories in figure 4. Grade 3 solicited reactions were reported by 196 (8·1%; 95% CI 7·0–9·3) of 2420 vaccine recipients and 118 (4·9%; 95% CI 4·1–5·9) of 2403 placebo recipients within 7 days after any injection, with comparable frequencies after dose 1 and dose 2 in the vaccine group (table 2; appendix pp 34–35). The proportion of medically attended adverse events reported was similar in the vaccine (5·7%; 95% CI 5·1–6·2) and placebo (6·0%; 95% CI 5·4–6·6) groups. The proportion of adverse events of special interest (one in the vaccine group and one in the placebo group), serious adverse events (30 in the vaccine group and 26 in the placebo group), and deaths (four in the vaccine group and six in the placebo group) were less than 1% in both study groups; no adverse event of special interest, serious adverse event, or death was deemed to be treatment related. There were no reported cases of thrombosis with thrombocytopenia syndrome, myocarditis, pericarditis, Bell's Palsy, or Guillain–Barré syndrome, or other immune-mediated diseases.

Discussion

Current bivalent COVID-19 vaccines gained authorisation based on immunogenicity data; however, as real-world data are prone to bias related to patient behaviours and characteristics, the need for clinical trials remains.[19] In this phase 3 trial evaluating a bivalent vaccine containing both the ancestral (D614) and beta (B.1.351) variant S protein as a primary series during a period of predominant omicron (BA.1 and BA.2) circulation, the primary objective was met in all participants, demonstrating efficacy against symptomatic COVID-19 higher than 50%, with a lower bound of the 95% CI higher than 30%.

The epidemiological context for this clinical trial is markedly different from that of trials conducted at the outset of the pandemic.[20,21] A large proportion of participants enrolled in this study had serological evidence of previous SARS-CoV-2 infection, which is relevant in the current climate, in which the population is largely non-naive due to previous infection or vaccination, or both.[22–24] Thus, the vaccine efficacy of 75·9% against symptomatic COVID-19 in non-naive participants observed in this study at least 14 days after dose 1 is of particular relevance. These findings also suggest the potential use of the vaccine as a booster dose at this stage of the pandemic, when most of the population have already been exposed to the virus or have been vaccinated. The use of the bivalent vaccine as a booster in adults aged 18–55 years primed with the BNT162b2 (Pfizer–BioNTech) vaccine has resulted in significantly higher anti-D614G or anti-B.1.351

	Vaccine group (n=6472)		Placebo group (n=6450)	
	n/N	% (95% CI)	n/N	% (95% CI)
Participants experiencing at least one of the following within 30 min after any injection (safety analysis set)				
Immediate unsolicited adverse event	4/6472	<0·1% (0·0–0·2)	7/6450	0·1% (0·0–0·2)
Immediate unsolicited adverse reaction	4/6472	<0·1% (0·0–0·2)	6/6450	<0·1% (0·0–0·2)
Participants experiencing at least one solicited reaction within 7 days after an injection (reactogenicity safety analysis set)				
Solicited reaction	1398/2420	57·8% (55·8–59·7)	983/2403	40·9% (38·9–42·9)
Grade 3 solicited reaction	196/2420	8·1% (7·0–9·3)	118/2403	4·9% (4·1–5·9)
Solicited injection-site reaction	1130/2419	46·7% (44·7–48·7)	645/2403	26·8% (25·1–28·7)
Grade 3 solicited injection-site reaction	98/2419	4·1% (3·3–4·9)	43/2403	1·8% (1·3–2·4)
Solicited systemic reaction	1100/2420	45·5% (43·5–47·5)	823/2403	34·2% (32·4–36·2)
Grade 3 solicited systemic reaction	172/2420	7·1% (6·1–8·2)	109/2403	4·5% (3·7–5·4)
Participants experiencing at least one of the following up to analysis cutoff date (safety analysis set)				
Adverse event leading to study termination	5/6472	<0·1% (0·0–0·2)	5/6450	<0·1% (0·0–0·2)
Serious adverse event	30/6472	0·5% (0·3–0·7)	26/6450	0·4% (0·3–0·6)
Related serious adverse event	0/6472	0·0% (0·0–0·1)	0/6450	0·0% (0·0–0·1)
Death*	4/6472	<0·1% (0·0–0 ·2)	6/6450	<0·1% (0·0–0·2)
Adverse event of special interest	1/6472	<0·1% (0·0–0·1)	1/6450	<0·1% (0·0–0·1)
Related adverse event of special interest	0/6472	0·0% (0·0–0·1)	0/6450	0·0% (0·0–0·1)
Medically attended adverse event	366/6472	5·7% (5·1–6·2)	385/6450	6·0% (5·4–6·6)
Related medically attended adverse event	11/6472	0·2% (0·1–0·3)	7/6450	0·1% (0·0–0·2)
COVID-19-associated medically attended adverse event	67/6472	1·0% (0·8–1·3)	86/6450	1·3% (1·1–1·6)
Virologically confirmed SARS-CoV-2 infection or symptomatic COVID-19 (regardless of adjudication)†	928/6472	14·3% (13·5–15·2)	1181/6450	18·3% (17·4–19·3)

N refers to the number of participants with available data for the relevant endpoint (for solicited adverse events) and for the corresponding subgroup for unsolicited adverse events, and n refers to the number of participants experiencing the endpoint listed. The denominator for the reactogenicity subset was 4823 (ie, the first 2000 participants recruited to each trial group and all participants aged ≥60 years). *The four deaths in the vaccine group were due to angioedema (after carbimazole and propranolol administration), acute respiratory distress syndrome (negative COVID-19 test), chronic kidney disease, and gunshot wound. The six deaths in the placebo group were due to hepatic failure, inguinal hernia, desmoid fibromatosis tumour, oesophageal carcinoma, haemorrhagic enterocolitis, and septic shock. None of the deaths was considered related to the treatment. †Cases were collected for safety purposes and not necessarily laboratory confirmed.

Table 2: **Summary of safety outcomes in participants who received at least one injection (safety analysis set)**

pseudovirus neutralisation titres after the booster dose than anti-D614G titres after primary vaccination in controls, with an anti-D614G ratio of 2·34 (98·3% CI 1·84–2·96) and an anti-B.1·351 ratio of 1·39 (98·3% CI 1·09–1·77) for the bivalent vaccine.[25] Furthermore, the booster elicited cross-neutralising antibodies against omicron BA.2 (for adults primed with the BNT162b2 and mRNA-1273 [Moderna] vaccines) and against omicron BA.1 (in BNT162b2-primed participants).[25] Vaccine efficacy was not observed in naive individuals, although the number of participants in this subgroup was small. This finding is in line with that of a study by Anderson and colleagues,[26] which showed that one dose of the BNT162b2 vaccine elicits stronger antibody responses in individuals previously exposed to COVID-19 than two doses of BNT162b2 in those without previous infection. Notwithstanding this point, in the current situation, in which large numbers of people have been vaccinated and the virus is still circulating, we should also consider the possibility that many people could also be developing hybrid immunity to SARS-CoV-2, whereby immunity is formed by the combination of vaccination and infection.[27] Although data on hybrid immunity are currently scarce, the consensus opinion is that hybrid immunity confers greater protection than that obtained from either infection or vaccination alone.

The use of placebo as a comparator is the most scientifically rigorous way to assess the absolute efficacy of a vaccine candidate. This enabled us to perform safety comparisons and also to maintain the blinding of randomisation, allowing unbiased evaluation of clinical outcomes related to COVID-19 illness and SARS-CoV-2 infection in both the vaccine and placebo groups. Such an approach has been recommended by a WHO-organised consultation and validated in a real-world setting.[28,29] The regions and subgroups analysed in this study were those in which trials of head-to-head comparisons to demonstrate non-inferior efficacy with currently authorised COVID-19 vaccines would be very large and operationally challenging to conduct in a timely manner. During the surveillance period, the two major variants circulating were the omicron BA.1 and BA.2 subvariants and, to a lesser extent, the delta variant, with no cases of the more contemporary omicron BA.4 and BA.5 subvariants. Thus, the data reported here are the first assessment of the clinical efficacy of a COVID-19 variant vaccine against the omicron variant. Since sequencing results were unavailable in 44·0% of participants in the modified full analysis set after

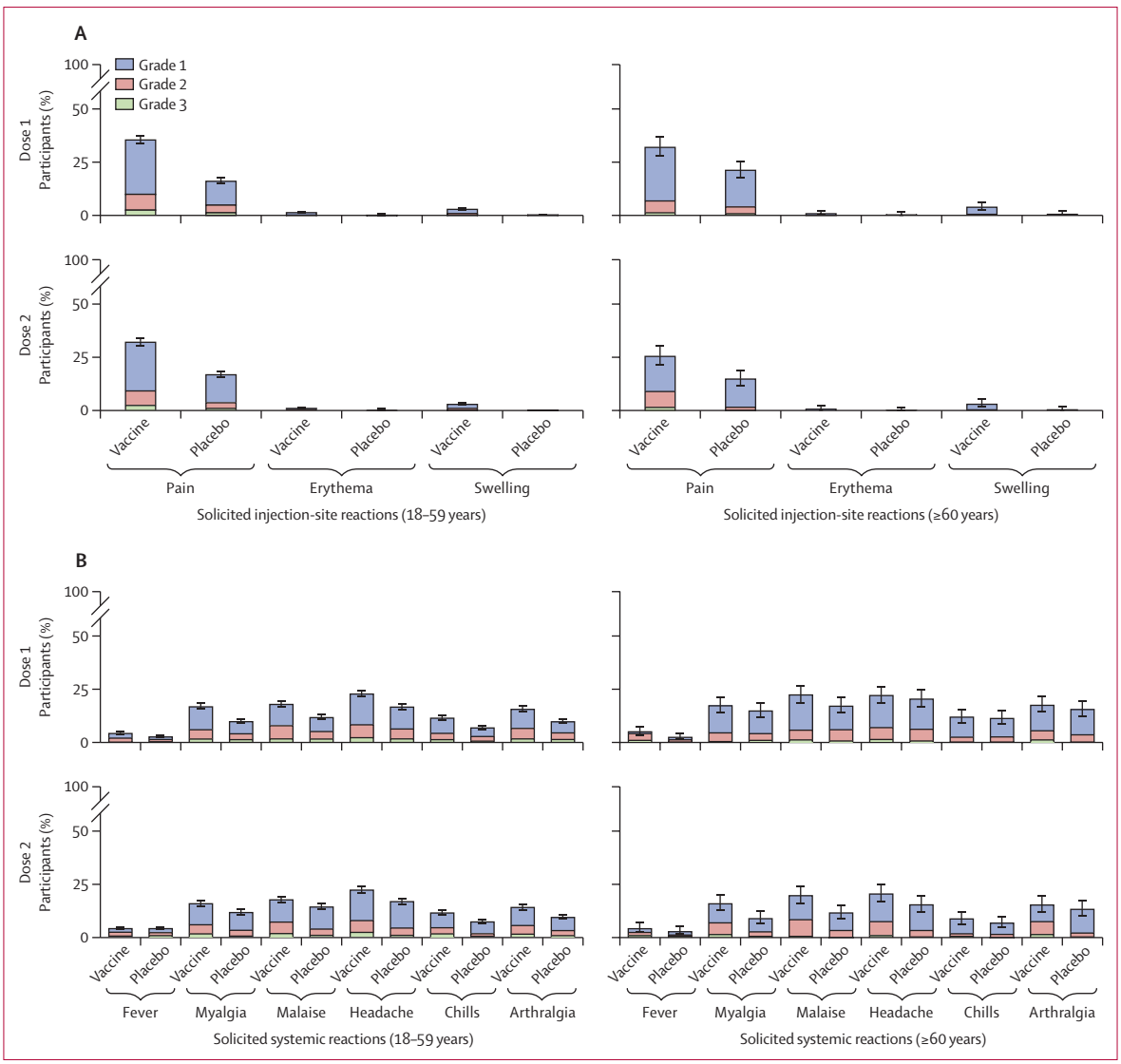


Figure 4: **Solicited injection-site reactions and solicited systemic reactions after each dose as per age categories**
(A) Proportion of participants with solicited injection-site reactions within 7 days of each study injection in participants aged 18–59 years and participants aged 60 years or older. (B) Proportion of participants with solicited systemic reactions within 7 days of each study injection in participants aged 18–59 years and participants aged 60 years or older. Error bars represent 95% CIs for any solicited reaction.

dose 2, we conducted sensitivity analyses that assumed these cases were caused by omicron variants, based on the temporal distribution of variants in the countries included in this study, and vaccine efficacy greater than our objective threshold of 50% was also demonstrated in these analyses.

The ability of three doses of the prototype vaccines (BNT162b2, ChAdOx1 nCOV-19 [Oxford–AstraZeneca], and mRNA-1273) to protect against symptomatic disease has been shown to be lower for the omicron variant (65·5% for BNT162b2, 48·9% for ChAdOx1 nCOV-19, and 75·1% for mRNA-1273) than for the delta variant (90·9% for BNT162b2, 82·8% for ChAdOx1 nCOV-19, and 94·5% for mRNA-1273), with effectiveness waning rapidly 20–25 weeks after the second dose.[30] By contrast, we showed efficacy against the omicron variant with two doses of a beta-containing variant vaccine as a primary series.

It has been shown previously that a BNT162b2 or mRNA-1273 booster after a primary course substantially increased protection against SARS-CoV-2, but this protection waned over time.[31] Variant-updated COVID-19 vaccines and booster vaccines incorporating omicron subvariants are currently under development or are authorised for use. Their use has been endorsed by global regulators, provided that novel COVID-19 booster vaccines containing alternative variants still confer adequate protection against omicron and other variants of concern. Our beta strain-containing vaccine confers

protection against omicron BA.1 and BA.2 variants that are not a component of the vaccine, thus providing clinical evidence that cross-protection might be conferred without a variant-chasing approach.[25]

In further support of broad cross-protection, it is clear that the protection provided by the original vaccines against new strains is insufficient; therefore, new formulations for booster vaccines were authorised for use in place of the original vaccines. Although the exact mechanism of cross-protection is unknown, it might be related to the B.1.351 component of the bivalent vaccine; however, there is no evidence directly supporting the view that inclusion of the beta variant improves cross-protection and it is possible that the prototypic strain alone might also contribute to the protective efficacy measured against omicron variants.[32–35] Substitutions in the beta variant spike at positions Lys417Asn, Glu484Lys, and Asn501Tyr might provide new antibody epitopes that are well positioned to provide cross-neutralising immunogenicity against a wide array of variants including contemporary circulating strains.[13] The results of this study in omicron-confirmed cases suggests the potential for a beta variant-containing vaccine to be used as a part of a booster programme. A beta variant-containing vaccine (VidPrevtyn Beta) has now been recommended by the European Medicines Agency and in the UK as a booster in adults previously vaccinated with an mRNA or adenoviral vector COVID-19 vaccine. Results from a booster study in individuals previously primed with the CoV2 preS dTM-AS03 (D614) vaccine or with other approved mRNA and adenovirus-vectored vaccines confirmed that a booster dose with a CoV2 preS dTM-AS03 (B.1.351, beta) vaccine delivered an immune response comparable to that of the bivalent (ancestral plus beta variant) booster.[25] Additionally, in a phase 1/2 randomised controlled trial, SCTV01C, a bivalent protein vaccine based on the spike protein sequences of SARS-CoV-2 alpha and beta variants, induced potent cross-strain neutralising antibody responses to non-vaccine variants, delta and omicron, when used as a booster in adults previously vaccinated with two doses (primary series) of an mRNA vaccine.[36]

The number of severe COVID-19 cases or hospital admissions due to COVID-19 in our study was small; however, all hospital admissions due to COVID-19 were observed in the placebo group. The few severe cases of COVID-19 and hospital admissions due to COVID-19 might have been due to the omicron variant, leading to milder COVID-19 versus other variants, particularly as most participants had already been previously exposed to SARS-CoV-2.[37] Additionally, most participants in this study were adults aged 18–59 years, with a lower risk of severe COVID-19 than those aged 60 years and older.[38,39] Notably, vaccine efficacy in participants aged 18–59 years with risk factors for severe COVID-19 was similar to that in the same age group without such risk factors (appendix p 29). We will continue to monitor the incidence of moderate or severe COVID-19 in participants as part of the long-term follow-up on the performance of the vaccine.

The bivalent vaccine showed an acceptable reactogenicity profile in this study; after both doses, adverse events were mostly mild to moderate and transient, regardless of participant age or previous infection. Injection-site and systemic reactions were each reported by less than half of participants in the reactogenicity subset. These rates might indicate potentially less reactogenicity compared with mRNA-based licensed vaccines (at least one injection-site reaction in 68·5% of participants after dose 1 and in 72·9% of participants after dose 2, or at least one systemic reaction in 50·6% of participants after dose 1 and in 69·5% of participants after dose 2 within 2 weeks of vaccination[40]), although these vaccines have not been evaluated together in the context of a single trial. No cases of myocarditis, pericarditis, or thrombosis with thrombocytopenia syndrome, which have previously been reported after vaccination with other vaccines, were reported during the observed 2–3 months of safety follow-up.[41,42] However, since these events are extremely rare (411 cases of myocarditis or pericarditis, or both, per 15 148 369 individuals aged 18–64 years;[43] and 15·1 cases of thrombosis with thrombocytopenia syndrome per million doses[44]), we would not expect to observe these events with the sample size of this study. Immunogenicity data are currently not available; these data will be published when they become available.

Our study had limitations. Due to the small number (approximately 6%) of adults aged 60 years and older enrolled in the trial, vaccine efficacy could not be accurately estimated in this age group (only three cases of symptomatic COVID-19 were reported in the vaccine group and two in the placebo group for adults aged ≥60 years). This was most probably due to the rollout of vaccines authorised for emergency use in this age category that were available at the time of the study. We acknowledge that the overall risk in individuals aged 18–59 years with medical issues is significantly lower than in populations aged 60 years and older, and not having data on individuals aged 60 years and older makes it difficult to generalise the potential for clinical benefit in the most at-risk populations. The small number of hospital admissions due to COVID-19 and severe cases of COVID-19 made it difficult to draw firm conclusions about vaccine efficacy against these outcomes, in contrast to efficacy data on severe COVID-19 for previously developed vaccines; however, data for previously developed vaccines were obtained from a SARS-CoV-2-naive population before the emergence of variants of concern.[45] To address this limitation, we will continue to monitor and report data on moderate and severe COVID-19 and on hospital admissions due to COVID-19. The short duration of follow-up (the median length of follow-up after dose 2 was 58 days) also precluded any firm conclusions on the

durability of the vaccine's protection and long-term safety, which we will also continue to monitor. Although sequencing was attempted on all viral strains isolated for the primary endpoint, results were available in only 68 (56·2%) cases. Sequencing data were available for 14 cases in the vaccine group and 54 cases in the placebo group. One explanation for this observation is the potential impact of the vaccine on reducing viral load. Although the higher rate of missing data in the vaccine group might bias variant-specific efficacy estimates, sensitivity analyses confirmed efficacy of the vaccine against omicron.

In conclusion, our results demonstrate the clinical efficacy of a beta variant-containing vaccine in protecting against different SARS-CoV-2 variants, including omicron (BA.1 and BA.2), with an acceptable safety profile in adults younger than 60 years. These data provide clinical evidence for a vaccination strategy to develop vaccines with an antigen from a non-predominant strain to confer cross-protection against newly emergent variants. These findings are particularly relevant in the current climate, in which more than 50 vaccines have been approved worldwide, but the addition of new vaccines to the current armamentarium will extend options to facilitate protection across different regions, health-care settings, and populations in the context of the ongoing pandemic, regardless of previous infection status, and with the threat of rapidly evolving SARS-CoV-2 strains.

VAT00008 Study Team

Karina Abalos, Jose Accini, Naveena Aloysia, John Humphrey Amuasi, Nana Akosua Ansah, David Benkeser, Aude Berge, Hanna Beyko, Oleksandra Bilotkach, Thomas Breuer, Alberto Cadena Bonfanti, Elisabeth Bukusi, Richard Canter, Jaime Augusto Carrillo, Danaya Chansinghakul, Florence Coux, Chandan Das, Santa Kumar Das, Louis Devlin, Luis Espinoza, Michael Fay, Dean Follmann, Carina Frago, Agnes Garinga, Peter B Gilbert, Claudia Gonzalez, Maria Angelica Granados, Lea Guillery, Ying Huang, Kathy Hudzina, Manish Jain, Piush Kanodia, Nitin Khandelwal, Cissy Kityo Mutuluuza, Francis Kiweewa, Noah Kiwanuka, Chalit Kosolsak, Darshna Kukian, Jitendra Singh Kushwaha, Thelma Laot, Eduardo Lopez-Medina, Hugo Macareno Arroyo, Kishorchandra Mandaliya, Stephanie Mamod, Somnath Mangarule, Javier Martínez, Scott McClelland, Lisa Menard, Sandra Mendoza, Satyajit Mohapatra, Catherine Moreau, Nelly Mugo, Videlis Nduba, Fernando Noriega, Patricia Nahirya Ntege, Brenda Okech, Maria Otero, Samuel Gurrion Ouma, Janet Oyieko, Mercedes Paredes, Erwin Pardo, Svitlana Postol, David Pekala, Penny Peng, Marie-Laure Py, Enrique Rivas, Rafael Rivero, Edith Rodriguez, Mansoor Saleh, Pedro Sánchez, Nessryne Sater, Jinen Shah, Rajeev Shrestha, Abraham Siika, Chandramani Singh, Veer Bahadur Singh, Dipesh Tamrakar, Fernanda Tavares Da-Silva, Lucas Otieno Tina, Hector Velasquez, Deo Wabwire, Anne Wajja, Elodie Zaworski, Nianxian Zhang.

For more on **Sanofi's data sharing criteria** see https://vivli.org/

Contributors

GHD, SRW, AC, JA, KPA, ASB, BF, KMN, LC, M-HG, MK-J, MLR, TT, CAD, SSa, SSr, and SG contributed substantially to the conception and design of the work reported in this Article. GHD, NR, SRW, AC, NG, MA, JA, KPA, ASB, TB, MIB, MC, MAC, BF, M-HG, MK-J, MJ, HK, MK, NLM, HR, MLR, FS, LS, TT, JT, TAW, CAD, RMC, SG, SSa, and SSr contributed substantially to data acquisition for the work reported in this Article. GHD, NR, SRW, AC, NG, MA, JA, KPA, ASB, TB, MIB, MA, MAC, DD, BF, M-HG, MK-J, MJ, JJK, HK, MK, RM, NLM, HR, MLR, SMVM, FS, LS, TT, JT, TAW, CAD, RMC, SG, SSa, and SSr contributed substantially to data analysis or interpretation of data for the work reported in this Article. AC, BF, and GHD have accessed and verified the data. All authors were involved in drafting or critically revising the manuscript, and all authors approved the final version and are accountable for the accuracy and integrity of the manuscript. All authors had full access to all the data in the study and accept responsibility for the decision to submit the manuscript for publication.

Declaration of interests

GHD, MIB, BF, M-HG, MC, JA, CAD, RMC, SG, SSr, and SSa are Sanofi employees. MIB, BF, M-HG, JA, CAD, RMC, and SSr hold stock or stock options in Sanofi. SG, RMC, and SSr hold patents pending on a COVID-19 vaccine. The Center for Vaccine Development and Global Health (CVD) receives grants from Pfizer to conduct clinical trials of COVID-19 vaccines. KMN receives no salary support for this grant. KMN receives grants from the US National Institutes of Health (NIH) to participate in overall organisation of COVID-19 vaccine trials and for participation in vaccine trials. RMC has received institutional funding from the Biomedical Advanced Research and Development Authority (BARDA) for the present study; has received support for attending meetings or travel, from Sanofi; and holds patents planned, issued, or pending from Sanofi. M-HG has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Sanofi. NR has received institutional funding from the NIH; and institutional grants or contracts from Merck, Sanofi, Quidel, Pfizer, and Lilly. SRW has received institutional funding from Sanofi and the National Institute of Allergy and Infectious Diseases (NIAID) and NIH; and institutional grants or contracts from Janssen Vaccines/Johnson & Johnson, Moderna Tx, Vir Biotechnology, and Worcester HIV Vaccine; has participated on data safety monitoring or advisory boards for Janssen Vaccines/Johnson & Johnson; and his spouse holds stocks and stock options in Regeneron Pharmaceuticals. NG has received institutional funding from Sanofi, GSK, and the NIAID and NIH; and is in receipt of grants or contracts from the NIH, NIAID, and the Division of AIDS (DAIDS). MA and TT are employees of NIAID, which funded aspects of the current study. LS, MAC, and MK are employees of GSK and own shares in the GSK group of companies. MJ and JJK have received institutional support from Sanofi and NIAID and NIH with respect to this study. MLR has received institutional support or contracts for the present manuscript from Walter Reed Army Institute of Research, Ingenuity Pathway Analysis, and the US Medical Research and Development Command. SSa was a Sanofi employee at the time of study conduct; and holds patents planned, issued, or pending on COVID-19 vaccines. LC has received grant funding from the NIAID/NIH. AC, KPA, ASB, TB, DD, MK-J, HK, RM, NLM, HR, SMVM, FS, JT, and TAW, declare no competing interests.

Data sharing

Qualified researchers can request access to participant-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report forms, statistical analysis plan, and dataset specifications. Participant-level data will be anonymised and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found online.

Acknowledgments

This study was funded by Sanofi, BARDA, and NIAID. NIAID provides grant funding to the HIV Vaccine Trials Network (HVTN) Leadership and Operations Center (UM1 AI 68614HVTN), the Statistics and Data Management Center (UM1 AI 68635), the HVTN Laboratory Center (UM1 AI 68618), the HIV Prevention Trials Network Leadership and Operations Center (UM1 AI 68619), the AIDS Clinical Trials Group Leadership and Operations Center (UM1 AI 68636), and the Infectious Diseases Clinical Research Consortium leadership group 5 (UM1 AI148684-03). We thank all participants, investigators, and study site personnel who took part in this study, including Kwame Ayisi Boateng and Anthony Afum-Adjei Awuah from the Ghana Health Service Kintampo Health Research Centre; Melvin Agbogbatey, Ebenezer Ahenkan, and Esther Daley Matey from the Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana; Claudia Pimentel from the Instituto Nacional de Pediatría, México;

Victor Mudhune Otieno, Grace Mugure Mboya, Zipporah Nyamoita Buko, and Taraz Samandari from the KEMRI CGHR Kisumu Kenya; Andrea Accini Valencia, Melissa Accini Valencia, Andrea de Moya, and Yineth Conrado from the IPS Cenatro Cientifico S.A.S, Colombia; Kenneth K Ngure, Eddah Mbugua, Stanley Ndwiga, Stephen Maina Gakuo, Philip Mwangi, David Chege, Jacinta Nyokabi, and Mercy Nyawira from the PHRD-Thika KEMRI Clinic, Thika, Kenya; Nichlous Ssebudde, Mary Grace Nalubega, Jenifer Alaba, Emmanuel Obonyo, Raymondo Oola, Harriet Tino, Geoffrey Magombe, Vanon Kyehayo, Ritah Norah Nalybwama, Rebecca Asiimire, Denis Wokorac, Agnes Alimo, and Abigail Link from the SICRA site at Lira Regional Referral Hospital, Lira, Uganda; Korutaro Violet, Elyanu Peter James, Baguma Allan, Kekitiinwa Adeodata, Sekabira Rogers, Ssebunnya Billy, and Ashaba Justus from the Baylor College of Medicine Children's Foundation-Uganda, Kampala, Uganda; Maricianah Onono, Imeldah Wakhungu, Kevin Onyango, Dismas Congo, Samya Rashid, Florence Ondiek, George Otieno, Job Ouma, Donnavane Ondego, Maqline Juma, Penina Amboka, Perez Odhiambo, Mildred Obare, Teresia Otieno, Caren Awinja, and Lizzie Kabete from the Kenya Medical Research Institute – Centre for Microbiological Research, Research Care and Training Program, Nairobi, Kenya; Lorena Buitrago from the Centro de Atencion e Investigacion Medica, Bogotá, Colombia; Patrick Ansah, Oscar Bangre, Michael Bandasua Kaburise, and Francis Broni from the Navrongo Health Research Centre, Navrongo, Ghana; Shelly Ramirez, Gail Broder, Liz Breisemeister, Jim Kublin, David Benkeser, and John Hural from the Fred Hutch Cancer Center, Seattle, WA, USA; Seyram Kaali, Samuel Harrison, Prince Agyapong, Felicia Serwah, Cynthia Bema, Elvis Eilson, Afia Korkor Opare Yeboah, Dennis Adu-Gyasi, Elisha Adeniji, Owusu Boahen, and Zakariah Buwah from the Research and Development Division, Ghana Health Service, Kintampo North Municipality, Kintampo, Ghana; and Oumou Maiga-Ascofare from the Kumasi Center for Collaborative Research in Tropical Medicine, Kumasi, Ghana. We also thank the Ministry of Health & Population, Government of Nepal, for providing swift approval to conduct this trial in Nepal. We acknowledge Steven Goodrick of inScience Communications (Springer Healthcare, London, UK) for providing medical writing assistance for the preparation of this manuscript, funded by Sanofi. We also thank Hanson Geevarghese for providing editorial assistance and manuscript coordination on behalf of Sanofi. Funding was provided by Sanofi and by federal funds from BARDA, part of the office of the Administration for Strategic Preparedness and Response at the US Department of Health and Human Services under contract number HHSO100201600005I, and in collaboration with the US Department of Defense Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense under contract number W15QKN-16-9-1002. The views presented here are those of the authors and do not purport to represent those of the US Department of the Army. This work was done in collaboration with GSK, who provided access to, and use of, the AS03 Adjuvant System.

References

1 Cai Y, Zhang J, Xiao T, et al. Structural basis for enhanced infectivity and immune evasion of SARS-CoV-2 variants. *Science* 2021; **373:** 642–48.

2 Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *Lancet* 2021; **397:** 1351–62.

3 Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med* 2021; **384:** 1885–98.

4 Shinde V, Bhikha S, Hoosain Z, et al. Efficacy of NVX-CoV2373 Covid-19 vaccine against the B.1.351 variant. *N Engl J Med* 2021; **384:** 1899–909.

5 Desai D, Khan AR, Soneja M, et al. Effectiveness of an inactivated virus-based SARS-CoV-2 vaccine, BBV152, in India: a test-negative, case-control study. *Lancet Infect Dis* 2022; **22:** 349–56.

6 Buchan SA, Chung H, Brown KA, et al. Estimated effectiveness of COVID-19 vaccines against omicron or delta symptomatic infection and severe outcomes. *JAMA Netw Open* 2022; **5:** e2232760.

7 Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 vaccine against omicron variant in South Africa. *N Engl J Med* 2022; **386:** 494–96.

8 Imai M, Ito M, Kiso M, et al. Efficacy of antiviral agents against omicron subvariants BQ.1.1 and XBB. *N Engl J Med* 2023; **388:** 89–91.

9 Chalkias S, Harper C, Vrbicky K, et al. A bivalent omicron-containing booster vaccine against Covid-19. *N Engl J Med* 2022; **387:** 1279–91.

10 Lin DY, Xu Y, Gu Y, et al. Effectiveness of bivalent boosters against severe omicron infection. *N Engl J Med* 2023; **388:** 764–66.

11 Pavot V, Berry C, Kishko M, et al. Protein-based SARS-CoV-2 spike vaccine booster increases cross-neutralization against SARS-CoV-2 variants of concern in non-human primates. *Nat Commun* 2022; **13:** 1699.

12 Goepfert PA, Fu B, Chabanon AL, et al. Safety and immunogenicity of SARS-CoV-2 recombinant protein vaccine formulations in healthy adults: interim results of a randomised, placebo-controlled, phase 1–2, dose-ranging study. *Lancet Infect Dis* 2021; **21:** 1257–70.

13 Sridhar S, Joaquin A, Bonaparte MI, et al. Safety and immunogenicity of an AS03-adjuvanted SARS-CoV-2 recombinant protein vaccine (CoV2 preS dTM) in healthy adults: interim findings from a phase 2, randomised, dose-finding, multicentre study. *Lancet Infect Dis* 2022; **22:** 636–48.

14 Dayan GH, Rouphael N, Walsh SR, et al. Efficacy of a monovalent (D614) SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant in adults: a phase 3, multi-country study. *EClinicalMedicine* (in press).

15 Garçon N, Vaughn DW, Didierlaurent AM. Development and evaluation of AS03, an adjuvant system containing α-tocopherol and squalene in an oil-in-water emulsion. *Expert Rev Vaccines* 2012; **11:** 349–66.

16 Shrestha L, Lin MJ, Xie H, et al. Clinical performance characteristics of the swift normalase amplicon panel for sensitive recovery of severe acute respiratory syndrome coronavirus 2 genomes. *J Mol Diagn* 2022; **24:** 963–76.

17 Joffe S, Babiker A, Ellenberg SS, et al. Data and safety monitoring of COVID-19 vaccine clinical trials. *J Infect Dis* 2021; **224:** 1995–2000.

18 FDA. Development and licensure of vaccines to prevent COVID-19: guidance for industry. June, 2020. https://www.fda.gov/media/139638/download (accessed May 19, 2023).

19 Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *J Gen Intern Med* 2011; **26:** 546–50.

20 Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; **384:** 403–16.

21 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2020; **383:** 2603–15.

22 Clarke KEN, Jones JM, Deng Y, et al. Seroprevalence of infection-induced SARS-CoV-2 antibodies — United States, September 2021–February 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 606–08.

23 Jones JM, Stone M, Sulaeman H, et al. Estimated US infection- and vaccine-induced SARS-CoV-2 seroprevalence based on blood donations, July 2020–May 2021. *JAMA* 2021; **326:** 1400–09.

24 Finch D, Tinson A. The continuing impact of COVID-19 on health and inequalities: a year on from our COVID-19 impact enquiry. August 24, 2022. https://www.health.org.uk/publications/long-reads/the-continuing-impact-of-covid-19-on-health-and-inequalities (accessed May 19, 2023).

25 de Bruyn G, Wang J, Purvis A, et al. Safety and immunogenicity of a variant-adapted SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant as a booster in adults primed with authorized vaccines: a phase 3, parallel-group study. *EClinicalMedicine* 2023; **62:** 102109.

26 Anderson M, Stec M, Rewane A, Landay A, Cloherty G, Moy J. SARS-CoV-2 antibody responses in infection-naive or previously infected individuals after 1 and 2 doses of the BNT162b2 vaccine. *JAMA Netw Open* 2021; **4:** e2119741.

27 Gavi, The Vaccine Alliance. Hybrid immunity: a combination of vaccination and prior infection probably offers the best protection against COVID. June 13, 2022. https://www.gavi.org/vaccineswork/hybrid-immunity-combination-vaccination-and-prior-infection-probably-offers-best (accessed June 2, 2023).

28 WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation. Placebo-controlled trials of Covid-19 vaccines—why we still need them. *N Engl J Med* 2021; **384:** e2.

29 Sisa I, Noblecilla E, Orozco F. Rationale to continue approving placebo-controlled COVID-19 vaccine trials in LMICs. *Lancet* 2021; **397:** 878.

30 Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med* 2022; **386:** 1532–46.

31 Andrejko KL, Pry JM, Myers JF, et al. Waning of 2-dose BNT162b2 and mRNA-1273 vaccine effectiveness against symptomatic SARS-CoV-2 infection accounting for depletion-of-susceptibles bias. *Am J Epidemiol* 2023; **192:** 895–907.

32 Lau JJ, Cheng SMS, Leung K, et al. Real-world COVID-19 vaccine effectiveness against the Omicron BA.2 variant in a SARS-CoV-2 infection-naive population. *Nat Med* 2023; **29:** 348–57.

33 Tsang NNY, So HC, Cowling BJ, Leung GM, Ip DKM. Effectiveness of BNT162b2 and CoronaVac COVID-19 vaccination against asymptomatic and symptomatic infection of SARS-CoV-2 omicron BA.2 in Hong Kong: a prospective cohort study. *Lancet Infect Dis* 2023; **23:** 421–34.

34 Glatman-Freedman A, Hershkovitz Y, Dichtiar R, Rosenberg A, Keinan-Boker L, Bromberg M. Effectiveness of BNT162b2 vaccine against omicron variant infection among children 5-11 years of age, Israel. *Emerg Infect Dis* 2023; **29:** 771–77.

35 Zou Y, Huang D, Jiang, et al. The vaccine efficacy against the SARS-CoV-2 omicron: a systemic review and meta-analysis. *Front Public Health* 2022; **10:** 940956.

36 Hannawi S, Saifeldin L, Abuquta A, et al. Safety and immunogenicity of a bivalent SARS-CoV-2 protein booster vaccine, SCTV01C, in adults previously vaccinated with mRNA vaccine: a randomized, double-blind, placebo-controlled phase 1/2 clinical trial. *EBioMedicine* 2022; **87:** 104386.

37 Meo SA, Meo AS, Al-Jassir FF, Klonoff DC. Omicron SARS-CoV-2 new variant: global prevalence and biological and clinical characteristics. *Eur Rev Med Pharmacol Sci* 2021; **25:** 8012–18.

38 Zhang H, Wu Y, He Y, et al. Age-related risk factors and complications of patients with COVID-19: a population-based retrospective study. *Front Med* 2022; **8:** 757459.

39 Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. *Eur J Epidemiol* 2020; **35:** 1123–38.

40 Chapin-Bardales J, Myers T, Gee J, et al. Reactogenicity within 2 weeks after mRNA COVID-19 vaccines: findings from the CDC v-safe surveillance system. *Vaccine* 2021; **39:** 7066–73.

41 Husby A, Køber L. COVID-19 mRNA vaccination and myocarditis or pericarditis. *Lancet* 2022; **399:** 2168–69.

42 Hafeez MU, Ikram M, Shafiq Z, et al. COVID-19 vaccine-associated thrombosis with thrombocytopenia syndrome (TTS): a systematic review and post hoc analysis. *Clin Appl Thromb Hemost* 2021; **27:** 10760296211048815.

43 Wong HL, Hu M, Zhou CK, et al. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. *Lancet* 2022; **399:** 2191–99.

44 Medicines & Healthcare products Regulatory Agency. Coronavirus vaccine – weekly summary of Yellow Card reporting. Updated March 8, 2023.https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting (accessed July 21, 2023).

45 McIntyre PB, Aggarwal R, Jani I, et al. COVID-19 vaccine strategies must focus on severe disease and global equity. *Lancet* 2022; **399:** 406–10.